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Multiple Molecular Pathways Unfolding the Pathophysiology of Polycystic Ovary Syndrome

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Abstract

Due to the abnormally elevated amounts of androgens women infected thruPolycystic ovary syndrome (PCOS) will practiceindications such as acne, hair loss, and obesity. Around 20% of women of reproductive age are impacted by it.Clinical symptoms include menstrual irregularities, miscarriages, dysfunction of follicular maturation, polycystic morphology of ovaries, obesity, acne, alopecia and hirustism**.**Previous studies have shown that PCOS women remainby high risk for metabolic and cardiovascular disorders as well cancers of reproductive system. Any disturbance of orchestrated chain of hormonal and genetic events can progress towardspolycystic ovaries and associated flaws. Expressions of certain genes such as sirtuins, chromobox homolog 2 (CBX2), kisspeptin, micro RNAs etc can immensely manipulate hyperandrogenism and/or hyperinsulinemia. Enhanced cytokine levels and related signaling pathways also emergein the pathophysiology of PCOS. The purpose of suchrevisionremains to explore the hormonal, biochemical, inflammatory, novel genomic and neuroendocrine profiles alliedthruPCOS that might lead towards the deeper understanding of this condition. This illumination can conquer new battlegrounds for the creation of possible and highly successful therapeutic strategies to improve the management of this syndrome and to minimise the risk of long-term complications. Simultaneously, high prevalence of pathological parameters among PCOS women also necessitates an early-stage diagnosis to control the high morbidity rates associated with it.

Key words: Polycystic ovary syndrome, hyperandrogenism, insulin resistance, obesity, Toll-like receptors, sirtuins, kissepeptin.

INTRODUCTION

Polycystic ovary syndrome (PCOS) remains a debilitating and life-long gynaecological endocrine condition such presents with extreme adverse effects on a woman's health and mental wellness **(Tabrizi et al., 2020; Glintborg and Andersen 2017).** Depending uponthe diagnostic criteria, approximately 20% of reproductive-age women are affected by PCOS **(Lizneva et al., 2016)**. Due to the exciting rise in the incidence of high prevalence craft, it has become the most prevalent endocrine condition in pre-menopausal people. Polycystic ovarian syndrome is mostly attributed to hormone imbalances and hereditary influences. The modified Ferriman–Gallwey (mFG) score is used to determine clinical hyperandrogenism**(Teede et al., 2018; Chen et al., 2008)**. Obesity, insulin resistence, hyperandrogenism and low vitamin D levelremaincontemporary in further than 50% of patientby PCOS **(Glintborg and Andersen, 2017)**. Along with these, inflammation

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(Alanbayet al., 2012; Kebapcilaret al., 2014), angiogenesis **(Oszet al., 2014)**, exercise **(Hakimi and Cameron, 2017)** and oxidative stress **(Piotrowski et al., 2005)** actively participate in pathogenesis of PCOS. Different studies have shown that PCOS women remain at high risk for metabolic and cardiovascular ailments**(Carvalho et al. 2017a)**. Growing clinical, experimental and genetic evidences also underlined the purpose of neuroendocrine structurein the pathogenesis of PCOS **(Witchel et al., 2019)**.

With the advancing of years, several scientific projects have been undertaken in pursuit of an exact pathogenesis and aetiology of PCOS **(Dumesic et al., 2015; Dunaif, 2016)**. Based on multiple hypotheses, numerous therapeutic modalities targeting androgen suppression and/or blockade, metabolic abnormalities, obesity, endometrial protection, reproductive therapies are employed **(Azziz R, 2016)**. Clinically, clomiphene citrate, metformin hydrochloride, combination of clomiphene citrate and metformin hydrochloride, hormonal therapy, rosiglitazone, and pioglitazone etc have been approved for the treatment of PCOS **(Cunningham, 2017;Ibanez et al., 2017; Khan et al., 2019)**. But the interval in the accepting of the pathogenesis andinappropriate managementof PCOS are still a foremost area of active research.

This review purposes to conferdifferent molecular alleywayssuch as hormonal, metabolic, inflammatory and novel genomic outlinesalliedthru PCOS. All these mechanismsmightsubsidizetowards the restoredconsideratearoundsuch syndrome and may inspire for the development of potential as well as highly efficient therapeutic strategies to improve management of PCOS.

Historical aspects and Diagnostic criteria for PCOS

Different diagnostic phenotypes used forrecognition of PCOS in women are summarized in **Table 1**. An Italian scientist Vallisneri (1721) described the histology of polycystic ovary with white shiny surface in infertile woman **(Insler and Lunesfeld, 1990)**. Chereau and Rokitansky(1844)unfolded sclerotic and fibrous changes of degenerative follicle within ovaries. Later on, description of bearded women was described by Achard-Thiers (1921).

In 1935, Irving Stern and Michael Leventhal first time distinct PCOS in hirsute, obese and amenorrheic women presenting chronic anovulation and enlarged ovaries along with many immature follicles **(Szydlarska et al., 2017)**. Then, Cooper and colleagues first time opened the genetic environment of PCOS **(Cooper et al., 1968).** Much later in 1990, the indicativemeasures for PCOS were redefined and re-discussed thru National Institute of Health (NIH) such biochemical hyperandrogenism associates with amenorrhea or oligomenorrhea**(Zawadzki and Dunaif, 1992).**

A few years later in 2003, Rotterdam consensus in collaboration with American Society of Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) expanded the initial NIH measures**(Ding et al., 2017)**. These revised criteria were established in 2004 to facilitate the obligation of sonographic presence of polycystic ovaries for PCOS diagnosis along with other key manifestations such as hyperandrogenism or extreme body hair or recurrent/ lacking menstrual cycle**(The Rotterdam, 2004)**. Moreover, Androgen Excess Society (AES) 2006 issued a statement with

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evidences that hyperandrogenism is a major culprit that predisposes the pathway for reproductive complications (like menstruation disorders, infertility, acne, hirsutism, and androgenic alopecia), metabolic complications (such as increased cardiovascular risk, insulin resistance and dyslipidemia) and ovarian or endometrial tumours **(Jayasena and Franks 2014)**.

Clinical presentation of PCOS

PCOS includes an extensive collection of symptoms that can divergethru age, weight and ethnicity. Clinically, this burden is characterized by menstrual irregularities, miscarriages **(Palomba et al., 2015)**, dysfunction of follicular maturation, polycystic ovaries, signs of hyperandrogenism and dysregulation of hormones certain as luteinizing hormone (LH) and follicular-stimulating hormone (FSH) subsequent in obesity, acne, alopecia and hirustism**(Yang et al., 2018).**The percentage of clinical symptoms is illustrated in **Figure 1.** Connotation of PCOS by infertility remains one of the most relevant complications assumedtowardsremainsliable for 40-70% of female infertility **(Sirmans and Pate, 2013)**. Furthermore, it remains a foremostsource of ovarian, endometrial and breast carcinomas. Moreover reproductive deviations, PCOS remains also sturdilyalliedthrough anextensivearray of metabolic ailments, certain as hepatic steatosis, dyslipidemia, glucose prejudice, diabetes mellitus type II (T2DM) and cardiovascular dysfunction **(Chandrasearan and Sagili, 2018)**. Androgen excess may rarely cause Cushing's syndrome, acromegaly and hyperprolactinemia. Thus, PCOS places heavy drains on health-care meanssuchmightsurpass $14 billion annual budgets in the US only. Because of heterogeneity in clinical symptoms of PCOS, all of these conditions not only stated the vast phenotypic variability**(Catteau-Jonard et al., 2012)** but also poses its long lasting deleterious and devastating effects on psychological well-being of women.

Clinical Prevalence and Pathogenesis of PCOS

Hyperandrogenism responsible for immature follicles, cyst formation, infertility and various cosmetic changes

Clinically, hyperandrogenism was defined with modified Ferriman–Gallwey (mFG) score ≥8. At least one abnormal value of serum androgens out of free testosterone >6 pg/mL, total testosterone >0.8 ng/dL, or dehydroepiandrosterone sulphate (DHEAS) >350 μg/dL is required to describe hyperandrogenism**(Teede et al., 2018)**.

Modification in androgenic milieuremains avital pathological property of PCOS escorting towards reproductive, metabolic and cosmetic deviations in women. These changes negatively influence the eminence of life of women thru PCOS **(Wojciechowska et al., 2019)**. Any disturbances at hypothalamic–pituitary–adrenal (HPA), hypothalamic–pituitary–ovary (HPO) and glands' axes function can primetowards androgen surplus and/or anovulation **(Figure 2)**. Epidemiologic studies have been reported inconsistent results for prevalence of PCOS. Hirsutism, acne or alopecia is main clinical feature of hyperandrogenism **(Hatch et al., 1981)**. However, ethnic variations may result in more or less hairy symptoms with similar serum androgen levels as compared to other population. The incidence of acne and androgenic alopecia in PCOS women is 16% and 2% respectively

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whereas prevalence of infertility varies in the range between 70-80% **(Jian et al., 2018)**. A hirsutism study was assessed in 531 Thai women and less than 3% of women (n=11) obtainablemFG score of ≥ 3, were deliberated as abnormal **(Cheewadhanaraks et al., 2004)**. In an another Chinese cross-sectional revision, 10% out of 2988 women of reproductive age exhibitedmFG scores of ≥5**(Zhao et al., 2011)**.

Normally, androgens are synthesized in ovarian pre-antral follicle theca cells and zona fasciculata of the adrenal cortex of adrenal glands. Interestingly, androgens contribute in equal ratio to upholdadvance of pre-antral and antral follicles.Pre-antral and antral follicles persuade granulosa cell FSH receptor appearance in initial antral follicle and to circulate testosterone during reproductive-age respectively **(Magoffin, 2005)**. In the ovarian granulosa cells, aromatase enzymeconverts theca cell-derived androgens into estradiol**(Figure 2)**. Altered aromatase activity in women with PCOS reduces this conversion of androgens to estradiol**(Chen et al. 2015)**. Hyperplasia of theca cells has been observed during follicle morphology of PCOS ovaries that may be an outcome of elevated androgen levels **(Magoffin, 2005)**.PCOS ovaries also show over-expressions of *CYP11A, 3-HSD* and *CYP17*enzymes and LH receptor in the theca cells thatpromote inherentsteroidogenicderegulation**(Rosenfield and Ehrmann, 2016)**.

Deficiency of FSH, hypersecretion of LH and elevated LH/FSH ratio are observed in around 55 to 75% of the women thru PCOS. Normally, discharge of gonadotrophin-releasing hormone (GnRH) is controlled by progesterone through negative feedback mechanism **(Rojas et al. 2014)**. But hyperandrogenism decreases the progesterone induced negative feedback mechanism. Henceforth, the persistent secretion of GnRH supports the surge of LH over FSH levels and eventually promotes LH/chorionic gonadotropin receptor*(LHCGR)*appearance in granulosa cell **(De Leo et al. 2016)**. Duringnormal ovarian folliculogenesis, the oocytes mainly mature under the influence FSH and LH to stimulate ovulation **(Cimino et al. 2016)**. However, disruption of this equilibrium disarrays the follicular development and induces establishment of immature oocytes prominenttowards infertility. In PCOS, high levels of LH articulate early luteinisation and form several premature antral follicles. Most of the follicles (2-5mm in diameter) stop at a small antral stage. Ovarian accumulation of these immature follicles disturbs the normal morphology of ovaries, results into formation of polycystic ovariesand anovulation in women thru PCOS **(Speroff et al., 2005)**.

Anti-Mullerian hormone (AMH) remains a glycoprotein veiledthrough granulosa cell of small growing follicle. AMH remains a member of the transforming growth factor b (*TGF b*) family and remainsveiled as a 140-kDa full-length homodimeric precursor and formerly cleaved thru prohormone convertase enzyme towardsproduce a 110-kDa pro N-terminal and 25-kDa mature C-terminal dimers allied non-covalently throughevery further**(di Clemente et al., 2010)**. This pro-mature non-covalent complex of AMH is biologically active form of AMH. It remains a vitalofficial of folliculogenesis in the ovaries. AMH acts on the primordial follicles to inhibitthe effects of FSH on growing follicles **(Weenen et al., 2004; Visser et al., 2006)**.Enhanced level of serum AMH mightremainpracticed as a biomarker for PCOS

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diagnosis **(Dewailly et al., 2016)**. High levels of AMH impair the follicle growth due to follicular resistance to FSH **(Palomaki et al., 2020)**. Furthermore, AMH resists FSH-inducedandrogen conversion to estradiolthrough aromatase conversion activity and contributes to hyperandrogenism in PCOS **(Chang et al. 2013; Eilertsen et al., 2012)**. It devoursstood studied such serum level of AMHmight be proportionate thru the quantity of ovarian follicle and cysts. Consequently, AMH mightremainpracticed as potential biomarker towardsdistinguish polycystic ovarian morphology;suchremainssolitary of the measures for spotting PCOS **(Pigny et al., 2006)**.

Dehydroepiandrosterone sulphate (DHEAS), an adrenal androgen is secreted by zona reticularis has similarlystoodconveyed to upsurge in PCOS **(Sorensen et al., 2016)**. Its impostremains also important to eliminatefurther severe reasons of virilisation, such as adrenal carcinoma. Nevertheless, prolactin and thyroid stimulating hormone (TSH) should be assessed to distinguishfurthersources of anovulation.

The metabolic milieu contributes to hyperandrogenism and adipogenesis

PCOS remainsalliedthroughseveral metabolic syndromes distinct as obesity, dyslipidemia, type 2 diabetes mellitus (T2DM) and cardiovascular disorders etc. The predominance of these metabolic consequences is approximately threefold greater in PCOS women in comparison to any other condition. Khorshidi et al. used 46 studies toshow the greatpredominance (30%) of metabolic syndromein PCOS **(Khorshidi et al., 2019)**. This organised revisionexplainedthe role of increased weight and oxidative stress in the advance of metabolic syndrome. A meta-analysis conducted by Zhao has clearly indicated the relationship between coronary heart diseases and PCOS **(Zhao et al., 2016)**.

Insulin resistance (IR) remains a key property inpathophysiolgy of PCOS and a major cause of excessive adipogenesis in specific women **(Morciano et al., 2014)**. Mostly all PCOS cases have some extent of IR, as they have35-40% less insulin sensitivity as compared to normal one. IR patient must have at least one abnormal diagnostic value out of carbohydrate metabolic profiles such as fasting blood glucose ≥ 100 mg/dL, 2-hour glucose ≥140, fasting glucose and insulin ratio <4.5 or homeostatic measurement assessment-insulin resistance (HOMA-IR) >2 **(Legro et al., 1998)**.

Various *in vitro* and *in vivo*revisions suggested such insulin synergize thru LH to upsurge theca cell androgen creation**(Rice et al., 2005)**. IR and compensatory hyperinsulinemia promotes the occurrence of hyperandrogenemiathroughsubstitute on the pituitary gland, ovaries, and liver **(Figure 3)**. Circulating insulin acts at the pituitary gland to upsurge gonadotropic compassion towards GnRHto potentiate steroidogenesis**(Baillargeon and Nestler, 2006).** It also enhances adrenal androgen secretion through stimulation of adrenocorticotropic hormone. Thereafter, reduced sex hormone binding protein (SHBG) levels in serum causes increase in free androgen concentration **(Diamanti-Kandarakis and Dunaif, 2012; Rosenfield and Ehrmann, 2016)**.

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Current human living style with virtual food abundance and sedentary lifestyle predisposed the people towards metabolic syndrome and its detrimental outcomes. Overweight and obesity remainforemost health distressesamid adolescent girls and adult women by PCOS. Nutrient surplusmight cause hypertrophy and/or hyperplasia of adipocytes that institutes a microenvironment consideredthroughIR, proinflammatory cytokine secretion, free fatty acid excessandmacrophage conquest**(Virtue and Vidal-Puig, 2010)**. In adipocyte, the reduced lipolysis triggersan augmentin serum free fatty acids (FFAs) and triglycerides, eventuallyforemost to amplified hepatic *denovo*lipogenesis and hyperlipidemia**(Samuel and Shulman, 2016)**. Enhanced lipid storage capacity of adipose tissue promotes fat storage in skeletal muscles, liver and pancreas. Elevated serum levels of FFAs inactivate pyruvate dehydrogenase (PDH) enzyme or reduce glucose transport action to exacerbate IR **(Ibanez et al., 2017)**. This process reduces insulin receptor substrate-1 (IRS-1) allied PI3 kinase actionsuch alters insulin signalling and reduces hepatic synthesis of SHBG **(Figure 3)(Samuel and Shulman, 2016)**. Furthermore, activity of ovarian P450c17 and P450scc enzymes is directly stimulated by circulating insulin which also promotes ovarian androgen steroidogenesis**(Genazzani, 2016)**.More interestingly, level of leptin (a hormone producedafter the adipose tissue) remains alsoinstitutetowardsremaineminent in women thru PCOS **(Brzechffa et al., 1996)**. Previous revisionsobligate revealed such leptin might alter the LH levels directly by stimulating GnRH**(Cimino et al. 2016; Lebrethon et al., 2000)**.

Many PCOS women exhibitvariations in the functionality of glucose transporter-4 (GLUT-4), suchremainscompulsory for glucose uptake into the cell**(Moran et al., 2010).** Furthermore, the formation and amassing of progressive glycation end products (AGEs) devoursremained reported to progress in PCOS patients. Moreover, AGEs interrelateby a cell surface receptor, receptor for AGEs (RAGE). The resultant over-expression of RAGE mainly interferes withinsulin-signaling and glucose metabolism in insulin-sensitive cell and tissuecomprising ovarian cell**(Ramasamy et al. 2012)**. AGEs rapidly activatevarious RAGE-signaling pathways certain as nuclear factor kappa B (NF-Kβ),endothelial cell-derived nitric oxide (NO), protein kinase C (PKC) and mitogen-activated protein kinase (MAPK)alleyways,suchcause to overproduction of reactive oxygen species (ROS), formation of toxic byproduct of NO (peroxynitrite), activation of NADPH oxidase and release of inflammatory marker respectively. **(Figure 3)**.Under oxidative environment, the stimulation ofRAGE cascade auxiliary exacerbates oxidative stress and inflammation through a positive feedback loop **(Ramasamy et al. 2012; Vlassara et al. 2002)**. Morphologically, it has been approved thatover-expression of RAGE in adipocytes is alliedthrough a decline in GLUT-4 gene expression and attenuation of insulin-signaling**(Monden et al. 2013)**.

IR can also enhance AMH concentrations and may contribute to elevate androgen levels in PCOS. La Marca et al. suggested a direct associationamid serum AMH and insulin resistance through Homeostatic Model Assessment (HOMA-IR) **(La Marca et al., 2004a)**. Fonseca et al. steered a cross-sectional revision and found a significant rise in AMH concentrations in PCOS patientby IR in contrast to PCOS patientdeprived of IR **(Fonseca et al., 2014)**.IR and endothelial dysfunction remainalliedby PCOS.Amplified synthesis of vasoconstrictors and

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reducedvasodilatationsimilarlyupsurges the risk of cardiovascular metabolic ailments in PCOS. These aspectsmightintensify the advance of IR in women by PCOS.

Role of inflammation in PCOS

A great immune response is required for normal folliculogenesis, ovulation and corpus luteum formation **(Gallinelli et al., 2003)**. Any alteration in ovarian immune cells and follicular cytokines mightreason for the inception and sternness of inflammatorysigns**(Wu et al., 2007)**. Enduring inflammation shows a centralpart in the pathogenesis of PCOS**(Figure 4)**. It devoursstoodinstitutesuch serum and follicular fluid intensities of inflammatory markercertain as C-reactive protein (CRP), tumor necrosis factor (TNF), interleukin-6 (IL-6), interleukin-18 (IL-18), monocyte chemotactic protein-1 (MCP-1) and acute phase serum amyloid A (APSAA), uplift in women through PCOS **(Alanbay et al., 2012; Aytan et al. 2016; Soter et al. 2015)**. Polymorphism of genes coding for TNF-α, IL-6 and their receptorssimilarlyalliedthrough PCOS**(Repaci et al. 2011; Carvalho et al. 2017b)**.

Oxidative stress and IR remain closely allied and mightprompt inflammatory retortthroughliberating inflammatory mediators and pro-inflammatory cytokine**(Gonzalez et al., 2006; Evans et al., 2005)**.Artimani et al. have executed a revision by using follicular fluid sample of 21 PCOS women **(Artimani et al., 2018)**. These studies have examined the oxidative stress and observed the higher concentrations of malondialdehyde (MDA) and total oxidant status (TOS) in PCOS women as compared to normal controls and is closely linked with inflammatory consequences. Furthermore, a meta-analysis performed thruMurri et al.has also evaluated oxidative stress in 4933 PCOS patients **(Murri et al., 2013)**. Evidences suggested that thesepatients exhibited higher circulating concentrations of MDA, homocysteine, and asymmetric dimethylarginine (ADMA), decreased levels of glutathione and paraoxonase-1 and increased activity of superoxide dismutase in comparison to normal controls.

Inflammatory cytokines: Many previous investigations concluded that inflammatory cytokines extensively increase the production of androgens. The resultant hyperandrogenemia disrupts the developmental stages of ovarian follicles in PCOS. IR-induced hypertrophy and hyperplasia of adipocytes stimulate the supplementstructure and create inflammatory cytokines **(Wellen and Horamisligil 2013; Carvalho et al. 2018)**. TNF-α, an inflammatory marker alliedby tissue inflammation, takescapacity to uphold the propagation of mesenchymal cells of follicular tissue and production of androgen in rat**(Spaczynski et al., 1999)**. PlasmaTNF-α is found to be elevated in PCOS, whicharouses the phosphorylation of insulin-receptor substrate-1 (IRS-1) protein and lipolysis in adipocytes**(Figure 4)((Mahde et al. 2009; Thathapudi et al. 2014)**. IRS-1 phosphorylation contributes to IR by inhibiting the insulin-signaling pathway whereas enhanced lipolysis causes increase inflowing free fatty acids and mightsubsidizetowards the development of cardiovascular ailments and T2DM **(Kopelman 2000)**. IR also elevates IL-6 levels in obese and PCOS women, which in turns uplifts circulating testosterone levels **(Zheng and Li 2016)**.Anefficientevaluation and meta-analysis revisionspalpablysustainedsuchgreater IL-6 levelremainconsiderablyalliedby

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HOMA-IR and IL-6 levelmightremainanexpedientchecking biomarker for the prediction in PCOS women **(Peng et al. 2016)**.

Toll like receptors (TLRs): TLRremains a intimate of pattern recognition receptors (PRRs) suchidentify the pathogen-induced molecular outlines in the innate immune response throughpersuadingkinase-signalingforces and transcription factor activation **(Sadik et al., 2015)**. These receptors are localize in many tissues and cells such as adipose tissue, cardiac myocytes, dermal endothelial cell, intestinal endothelial cell, cumulus cell, granulosa cell, and theca cells. Studies have shown that TLRs are responsible for initiating the inflammatory response and inhibits insulin sensitivity, thereby promoting insulin resistance **(Hotamisligil and Erbay, 2008)**. The activation of the TLR2 and TLR4 is considered as an important factor of IR **(Kochumon et al., 2018)**. In PCOS, the TLR4-signaling could initiate inflammation through NF-Kβ pathway **(Figure 4)**. Previous preclinical data have also verified that disruption of TLR4-gene plays a protective role against obesity-induced inflammation and IR in mice **(Shi et al., 2006, Suganami et al., 2007)**. Obesity-induced FFAs could cause the sustained activation of TLR-signaling, which may impair insulin action. TLR4 signaling-induced activation of adipocytes and macrophages release various cytokine and chemokine like TNF-α, IL-1β, IL-6, MCP-1 and CRPssuchindorseinflammation. In addition, adipocytes remain abundant cause of leptin and adiponectinnearmaintain insulin sensitivity althoughstruggling and retinol-binding protein 4 (RBP4) towardsprejudice insulin sensitivity**(Schenk et al., 2008)**.

Novel gene families and neuroendocrine factors associated with PCOS

Exceedingly orchestrated restraint of genetic procedurescertain as multiple transcription factors and genetic circuits play anessentialpart in the ovarian advance. Any disturbance in organized network of genes can evoke many clinical complications including ovulation defects, polycystic ovariesand ovarian cancer. Genome-wide association studies (GWASs) correlated the pathogenic role of gonadotropins in PCOS via identification of genes involved in HPO-axis functioning such as LHCGR gene and FSHR gene **(Hayes et al., 2015)**. It has been known that the expressions of genes relevant to the development of PCOS are mainly influenced by hyperandrogenism and/or hyperinsulinemia.

Sirtuins: Sirtuinsbelong to deacetylases group thatcan change structural proteins, metabolic enzymes and histonesthrough directive of specific-gene expressions and activation and/or deactivation of other proteins to modifyfunction of cellular proteins**(Morris, 2013)**. In mammals, there are seven sirtuins (*SIRT1–SIRT7*) that exhibit a conserved catalytic domain in processes like DNA repair, maintenance of metabolic homeostasis, oxidative stress, aging-degeneration or cancer. Evidences suggested that post-ovulatory luteinized granulosa cells of human ovarian follicles express all these seven members of sirtuin-genefamily **(Tanno et al., 2007).** A clinical study conducted on IVF patients consist of different infertility diagnostic groups and oocyte donor groups providedthequantitative gene-expression of sirtuinsin luteinizing granulosa cell**(Zhao et al., 2014)**. The diverse patterns of sirtuinsexpressions found in this study reflected their role in pathological and physiological conditions. Study also revealed that sirtuins may exhibit protective and defensive mechanisms against various

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conditions due to their compensatory mechanism. Out of seven sirtuins,*SIRT1* has a great role ininflammation (via NF-κB activity), energy metabolism (via PPAR-γ regulation) and apoptosis (via inhibiting p53-dependent transcription) **(Zhang et al., 2010)**.*SIRT1,SIRT3, SIRT5* and *SIRT6* have been involved in apoptosis of ovarian granulose cellthrough follicular atresia and preservation of follicle reserve to increase ovarian function lifespan and fertility.*SIRT2, SIRT3 SIRT5* and *SIRT7*moves into mitochondria and participate in detoxification of ROS to protect cells from oxidative stress **(Gonzalez-Fernandez et al., 2019)**.

Androgen Receptor Gene (AR): ARremainscontemporary on chromosome Xq12 and has 11 exons. This gene has three functional domains and it can code for more than 90 kb long proteins**(Ajmal et al., 2019)**. Some studies explored that AR is an X linked gene and inactivation of X disrupts androgen-signaling pathway. It may be of great interest towardsbehaviour Genome ExtensiveConnotation for PCOS to recognize the innovativealterations of AR to expand genomic pathology of PCOS **(Urbanek, 2014)**.

Chromobox homolog 2 (CBX2): Recent studies have confirmed the presence of CBX2 genome in both male and female reproductive systems. This homolog of gene is a controller of homeotic gene appearancethroughinitial embryogenesis. Two isoform of CBX2 (*CBX2.1* and *CBX2.2*) obligatestood identified. *CBX2.1* contains a polycomb box whereas *CBX2.2* lacks the polycomb box **(Volkel et al., 2012)**. *CBX2.2* regulates expression of mitogen-activated protein 3-kinase 15 (*MAP3K15*) and Aldo-keto reductase family 1 member C1 (*AKR1C1*) through negative feedback mechanism. A preclinical study conducted on rats showed high MAPK expression patterns during secondary and antral follicle phasesover those in the primordial follicles or primary follicle**(Hu et al., 2017)**. Henceforth, we could be assumed that MAPK-signaling pathway possibly involved during growth and development of follicles whereas reduced levels of MAPK can significantly evoke excessive androgen production in women. Aldo-keto reductase steroidogenic enzymes (*AKR1C1-AKR1C4*) are present in adrenal and ovarian tissues and they regulatethe fabrication of androgens in adipose tissue in both males and females **(Marti et al., 2017)**. This pathway seems to be enhanced in the PCOS **(Del Valle et al., 2017)**. Biason-Lauber and co workers provided evidences regarding regulation of androgen receptor in the ovary via*AKR1C1* and *CBX2.2*expression **(Biason-Lauber et al., 2019)**. Supplementaryrevisionsremain still needed to expand the role CBX2 network to show how these new targets involved in ovarian functionality in humans.

MicroRNAs (miRNAs): Epigenetic modifications like variations in methylation and miRNAs open added more interesting theory of regulations distressing the PCOS phenotype **(Kokosar et al., 2019)**. The miRNA-regulated gene expression remainsdeliberatedtowardsstand an additional stratum of epigenetic guideline and intricate in the guideline of apoptosis; propagation and steroidogenesis in granulose cells. Circulating or ovarian miRNAs mightpossibly amend steroidogenesis and ovarian purpose in PCOS women. It has been identified that quantity of miRNAs dysregulated in PCOS**(Wu et al., 2014).** Some currentrevisionsobligaterevealed that miR-200c has been increased in granulose cells of

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cystic ovarieswhereas the expression of miR-324 and miRNA- 592 wereconsiderably downregulated in PCOS ovaries**(Song et al., 2015).**

***DENND1A*:**Genetic studies have recognized over expression of another interesting locus i.e.*DENND1A* during excessive production of androgens in theca cell and adrenal cell line. Nevertheless, the mechanismliable for amplifiedappearance of such modifiedresidues to remainexplicated**(Tee et al., 2016)**.

Kisspeptin: Kisspeptins (encoded by *KISS1* gene) are produced by Kisspeptin-1 neurons, which are master regulators of neurosecretion of GnRH and ovulation (**Osuka et al., 2017)**. Currentrevisionsobligaterevealedsuch kisspeptin-1 and its receptors remainuttered in the mammalian ovary and play a putative role in initiation of puberty, follicular development, oocyte maturation, steroidogenesis and ovulation through HPG-axis **(Hu et al., 2018)**. Temporal coupling of kisspeptin–LH pulse demands normal menstrual cycling, however in PCOS women loss of this coupling result in oligomenorrhea**(Katulski et al., 2018)**. Moreover, down regulation of *KISS1* leads to reproductive function failure and female infertility **(Topaloglu et al., 2012)**. Various revisionsobligateremainedsteered to identify *KISS1* neurons in diverse mammalian species, comprising humans, rodents, and non-human primates. Arcuate nucleus (ARC) of the mediobasal hypothalamus is highly conserved region for *KISS1* neuronal populations in humans. One interesting feature of *KISS1* neurons in the ARC remainssuch sex steroids reliablysubdue*KISS1* expression at this region through negative feedback. In contrast estrogenimproves*KISS1*manifestation at such site through positive feedback. Other neurotransmitters like neurokinin B (NKB) and dynorphin are also expressed in Kiss1 neurons and showforemostparts in the regulator of GnRH/gonadotropin secretion **(Navarro et al., 2012)**. Studies have reported that NKB and dynorphin significantly stimulate and inhibit LH secretion correspondingly. It devoursremaineddescribedsuch NKB and dynorphin contribute in the auto-regulation of kisspeptin-associated GnRH pulses however any dysregulated function of *KISS1*valoursubsidize to neuroendocrine variations of PCOS. In the rodent models of PCOS, determinedconquest of hypothalamic *KISS1* expression have been found due to postnatal exposure to androgens **(Brown et al., 2012).**

Galanin: Galanin, a neuropeptide is present throughout the central nervous system, peripheral nervous system and the reproductive system in both sexes **(Webling et al., 2012)**. It exhibits various physiological actions via its three members (GAL1, GAL2 and GAL3) of G-protein-coupled receptors (GPCRs) superfamily **(Mensah et al., 2018; Li et al., 2017)**. Hypothalamus contains a subset of GnRH-producing neurons that also help in synthesis of galanin. GAL2 has been widely distributed in the ovary **(Waters and Krause, 2000).** Various preclinical studies have been demonstrated such galanin shows a putative part in the group of the preovulatory LH flow and gonadal excretion**(Fang et al., 2015).** Dysregulation of gonadotropin in PCOS patients significantly indicated the role of galanin in development of this disease **(Roland and Moenter, 2014).**Evidences supported that galanin peptide could signifiantly reduce inflammatory marker (TNF-α, IL-6), an upsurge in FSH and a decline in LH, insulin and testosterone levels, henceforth may be an excellent therapeutic option for PCOS management.

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Risk of tumors of reproductive system

The altered metabolic and hormonal environment emerged the risk of cancer of reproductive system among women. The prolonged and unrestrictedestrogen in the absenteeism of adequate progesterone remainsstared as a chiefissue originating endometrial hyperplasia and/or endometrialcancer in PCOS **(Harris and Terry, 2016)**. Estrogen binding to its nuclear receptor leads to stimulation of countless growth issuescomprising insulin-like growth factor(IGF) and epidermal growth factor (EGF). These growth factors in turn activate extracellular-signal-regulated kinase(ERK)alleyway and uphold endometrial propagation and straightcancer. Moreover, estrogen metabolites likewise cause DNA damage through oxidative stress and could initiate endometrial cancer. Increased androgens have been associated to cause ovarian cancer among PCOS women **(Butler et al., 2013)**. It has been hypothesized that the incidence of androgen receptors on ovarian cells increased the risk of invasive ovarian and borderline tumors.

Current medications for the management of PCOS

Several treatment modalities include clomiphene citrate, metformin hydrochloride, combination of clomiphene citrate and metformin hydrochloride, hormonal therapy, rosiglitazone, and pioglitazone have been approved for the treatment of PCOS **(Cunningham, 2017; Zhang et al., 2017)**. However, resistance displayed by first line drug (clomiphene citrate) and long-term treatment regimen of other drugs with lesser clinical output **(Liao et al., 2011)** encourages the researchers to find other effective therapies in the treatment of PCOS. Oral metformin hydrochloride is widely used by the gynaecologists in the management of PCOS for induction of ovulation. Metformin hydrochloride impedes the GnRH release through stimulating hypothalamic AMP-activated protein kinase (AMPK) **(Kai et al., 2015)**. Despite, metformin hydrochloride is able to detains ovarian gluconeogenesis (production of glucose from non-carbohydrate carbon sources) and attenuates ovarian androgen production; it is always in controversy for gastrointestinal discomfort and lactic acidosis. Clinically, oral contraceptive pills (OCPs) remain first line choice for the supervision of hirsutism in premenopausal women **(Badawy and Elnashar, 2011).** OCP therapy exhibits number of side effects such as continuous headache, breast tenderness, risk of venous thromboembolism and incline to upsurge insulin confrontation. Moreover, antiandrogens have also been beneficial for the treatment of acne. Finasteride remains an antiandrogen drug suchconflictinglyconstrains both tissue and hepatic 5-α-reductase to prevent further conversion of androstenodioneto 5 α-androstane-3, 17- dione**.** Spironolactone remains an aldosterone antagonist and androgen receptor blocker, which is also responsible for inhibiting ovarian and adrenal steroidogenesis. But irregular menstrual bleeding, headache, hypotension, nausea, declined libido and feminization of male foetuses are major limitations of this therapy.

CONCLUSION

PCOS remains the collective gynaecological illness affecting 1 in 5 women of reproductive age. The pathophysiology has involvement of complex molecular alleywaysbycompound mechanisms certain as hormonal, metabolic, inflammatory, genetic and neuroendocrine

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hemostaticvariations. This review deliberated the diverse key sorts for the same to inspire new treatment strategies in the therapy of PCOS as a replacement for of indicativemanagement. Furthermore, signaling pathways and genetic environment has been deliberatedin this assessmenttoadvance the considerate of pathophysiological aspects of PCOS. It remainslikewisecompulsory for futuretowards shed light on the more genomic environment and cellular pathways alliedthrough the pathogenesis of PCOS if any.

Declaration of Interest

The authors have declared no conflict of interest. The authors alone are responsible for content and writing the paper.

Author Contributions

S.K.C, P.G and R.K.Shas designed and conceptualised the content. S.K.Cwrote the manuscript.No paper mill was used. All authors read and approved the manuscript.

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